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The relation of rhinitis to recurrent cough and wheezing: A longitudinal study

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KEYWORDS
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Summary
Background: Recurrent cough can be a clinical manifestation of rhinitis. However, it remains unclear if the association between rhinitis and recurrent cough among children is independent of asthma.
Objective: The aim of the present study was to determine, in a large longitudinal cohort, whether rhinitis is significantly associated with recurrent cough alone, wheezing alone, or the combination of both symptoms during childhood.
Methods: We investigated determinants of recurrent cough, with or without wheezing, using longitudinal data from the Tucson Children's Respiratory Study. Among the 1246 subjects originally enrolled, 1024 children completed at least one questionnaire between the ages of 6 and 18 years and were included in the present study. In any survey, wheezing was defined as at least one wheezing episode during the past year and recurrent cough as two or more coughing episodes lasting at least 1 week without a cold during the past year. Generalized estimating equations were used to determine significant risk factors.
Results: After adjusting for sex, skin test reactivity and parental asthma, both rhinitis (OR = 2.47 CI = 1.84, 3.30) and sinusitis (OR = 1.54 CI = 1.11, 2.14) were associated with an increased risk of recurrent cough plus wheezing. The OR associated with rhinitis were significantly reduced for subjects reporting only recurrent cough or only wheezing (OR = 1.43, CI = 1.03, 1.99; and OR = 1.30, CI = 1.07, 1.58, respectively). Recurrent cough and wheezing, when examined independently, showed different patterns of risk factors.
Conclusion: We found rhinitis to be an independent risk factor for both recurrent cough and wheezing during childhood. Different pathways may be involved in the association of rhinitis with recurrent cough and wheezing.

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Introduction

Recurrent cough, defined as repeated cough episodes apart from colds, is a frequent respiratory complaint and a common reason for seeking medical attention in childhood. In a study from Leicestershire, UK, among 1422 preschool age children, the overall prevalence of recurrent cough without colds was 21.8% and the rates showed a significantly increasing trend with age from a 18.9% in the first year of life up to 27.6% at age 5.[1] Findings from other cohorts[2,3] suggest that the point prevalence might be even higher among school-age children, although comparisons among different studies could have been affected by the way recurrent cough was defined. Recurrent cough can represent a troublesome condition in the pediatric clinical setting and its causes are often not found.

Children with asthma can present with recurrent cough, but isolated cough as the sole manifestation of asthma[4,5] without associated wheeze is rare. Both epidemiological and clinical studies suggest that recurrent cough can also be a clinical manifestation of rhinitis and sinusitis.[6] These last two conditions, however, also show a strong association with asthma,[7–10] and it thus remains unclear if the association between rhinitis and recurrent cough is a direct expression of the relationship between upper airway disease and asthma or if rhinitis is an important risk factor for recurrent cough independent of asthma.

The aim of the present study was to determine, in a large longitudinal cohort, whether rhinitis is significantly associated with recurrent cough alone, wheezing alone, or the combination of both symptoms during childhood, and whether these relations change over time between the ages of 6–18 years.

Materials and methods

Study population

A total of 1246 healthy infants born from May 1980 to October 1984 were enrolled in the Tucson Children's Respiratory Study. Their parents were patients of a large health maintenance organization in Tucson, Arizona. The study population included mainly Hispanic (20%) and non-Hispanic (75%) Caucasians, reflecting Tucson's population. More details on the study design, data collection, and procedures are presented elsewhere.[11] Children were evaluated for respiratory symptoms at several surveys between ages 6 and 18. Subjects were included in the current analyses if they had completed at least one of the six questionnaires conducted between these two ages.

Questionnaires

In each survey, questionnaires were completed by either the parent or child depending on the age of the participant. Questionnaires were based on a modified version of the 1978 ATS/DLD questionnaire. Children were classified as having *recurrent cough* in any survey if they reported having two or more coughing episodes that lasted at least 1 week without a cold in the past year. Likewise, children were classified as having active *wheezing* in any survey if they reported at least one wheezing episode during the past year. Subjects reporting both recurrent cough and wheezing during the same survey were classified as having *recurrent cough and wheezing*. Subjects were considered to have active rhinitis or sinusitis if they reported 'hay fever or any other allergy that made their nose runny or stuffy, apart from colds' or the presence of a physician confirmed 'sinus trouble', respectively. They also had to indicate that rhinitis or sinusitis was current or that they were currently taking a medication for it. Both rhinitis and sinusitis were assessed each survey and included in the analyses as time-dependent variables.

Parents' ethnicity, years of education, and asthma status were also determined from the questionnaires completed at enrollment. Ethnicity for each parent was characterized as non-Hispanic Caucasian, Hispanic and other. For years of education, a binary variable was created with less than or equal to 12 years of schooling as the reference group. Parents were also asked during survey 6 if they currently smoked cigarettes. This was included as a binary indicator variable for each parent with non-smokers as the reference group.

Skin tests

During three surveys taken at approximately 6, 11, and 16 years of age, subjects received allergy skin prick test to seven aeroallergens common in the Tucson area (house dust mix, olive, Bermuda grass, mulberry, mesquite, careless weed, and Alternaria). Histamine and a control consisting of 50% glycerine were also applied. Wheal size was recorded as the sum of the two diameters at right angles to each other (in millimeters). Subjects were considered positive in a given survey if at least one wheal was greater than 3 mm after

subtraction of the control value. Subjects were classified as *persistent skin test positive* if they were tested during at least two surveys and were skin test positive at each testing. They were classified as *late skin test positive* if they had two or more skin tests and had one or more negative test results followed by only positive test results. Subjects who had a negative test(s) after having a positive test were classified as *remitting skin test positive*. Only six subjects were included in this latter category so they were excluded from subsequent analyses. Subjects that were always skin test negative were coded as the *reference group*.

Statistical methods

Since the dependent variables, combinations of recurrent cough and wheezing, were longitudinal binary variables that were repeatedly determined at each survey, we used the generalized estimating equation (GEE) to determine significant risk factors. This statistical procedure adjusts for the serial correlation between repeated observations and allows subjects to have different numbers of observations under the assumption that missing observations are missing completely at random.

We examined three longitudinal outcomes independently: recurrent cough with wheezing, recurrent cough and no wheezing, and wheezing and no recurrent cough. Time-dependent co-variates included rhinitis, sinusitis, and age. Including either rhinitis or sinusitis as a time-dependent variable implies that the exposure or risk factor (e.g. rhinitis) is assessed concurrently with the symptom (e.g. wheezing). Sex, parental smoking at age 6 questionnaire, parental ethnicity, parental asthma status, parental education, and child's skin prick test results were included as fixed co-variates. Interactions between sex, age and combinations of risk factors were also tested. Candidate predictor variables were first tested in an exploratory or marginal analysis without any other predictor variables in the GEE. Variables that showed potential to be a predictor variable (i.e. $P \leqslant 0.1$) were then tested collectively in a combined model. The most parsimonious model was selected by backward elimination of non-significant variables and the best fitting co-variance pattern was selected using Quasi-likelihood Information Criteria (QIC).[12] All statistical tests were conducted at the $\alpha = 0.05$ significance level with two tailed comparisons.

Results

There were 1246 subjects who were enrolled in this study and 1024 who met the inclusion criteria. Table 1 shows the demographics for participants in the Children's Respiratory Study. There were nearly equal proportions of males and females; 22% of subjects were classified as persistent skin test positive and 15% were considered late skin test positive. Approximately 10% of the subjects had either a mother or a father who reported having asthma.

Table 2 lists the time-dependent variables included in the longitudinal analyses. Variables that are time-dependent in the longitudinal model, both dependent and independent variables, allow subjects to change their status between surveys.

Table 1 Descriptive statistics for fixed and baseline variables.

Variable	Frequency (%)	
Sex	Male	611 (49)
	Female	635 (51)
Mother smokes year 6	No	802 (82)
	Yes	180 (18)
Father smokes year 6	No	691 (78)
	Yes	191 (22)
Ethnicity of mother	Caucasian	915 (74)
	Other	79 (6)
	Hispanic	248 (20)
Ethnicity of father	Caucasian	818 (74)
	Other	74 (7)
	Hispanic	211 (19)
Skin test results		
Reference (negative)		646 (63)
Persistent positive		225 (22)
Late onset positive		148 (15)
Skin test positive (any)	No	646 (63)
	Yes	373 (37)
Mother has asthma	No	978 (90)
	Yes	113 (10)
Father has asthma	No	970 (89)
	Yes	121 (11)
Education: mother	$\leqslant$12 years	394 (32)
	$>$12 years	847 (78)
Education: father	$\leqslant$12 years	847 (78)
	$>$12 years	856 (70)

Study subjects were participants in the Children's Respiratory Study, Tucson Arizona.

Table 2 Descriptive statistics for time dependent variables for each survey.

Variable	Description	YR6	YR8	YR11	YR13	YR16	YR18
N	Sample size	1024	940	956	708	682	578
Age (mean $\pm$ SD)	Age at each survey questionnaire	6.27 $\pm$ 0.95	8.62 $\pm$ 0.72	10.9 $\pm$ 0.66	13.5 $\pm$ 0.65	16.6 $\pm$ 0.55	18.7 $\pm$ 0.71
Recurrent cough and wheezing	Duration $>$ 1week and $\geqslant$ 2 episodes w/o cold and wheezing	86 (8.4%)	93 (9.9%)	96 (10.0%)	56 (7.9%)	67 (9.8%)	64 (11.1%)
Recurrent cough and no wheezing	Duration $>$ 1week and $\geqslant$ 2 episodes w/o cold and no wheezing	62 (6.1%)	43 (4.6%)	58 (6.1%)	29 (4.1%)	46 (6.7%)	24 (4.2%)
Wheezing and no recurrent cough	Wheezing with $\geqslant$ 1 attack in past year and no recurrent cough	183 (17.9%)	117 (12.5%)	158 (16.5%)	121 (17.1%)	163 (23.9%)	157 (27.2%)
Rhinitis	Report rhinitis current and/or taking medications for treatment	294 (28.7%)	247 (26.3%)	292 (30.5%)	250 (35.3%)	166 (24.3%)	117 (20.2%)
Sinusitis	Report sinusitis current and/or taking medications for treatment	110 (10.7%)	90 (9.6%)	160 (16.7%)	144 (20.3%)	117 (17.2%)	123 (21.3%)

Study subjects were participants in the Children's Respiratory Study, Tucson Arizona.

Table 3 Results from fitting the longitudinal recurrent cough and wheezing combinations as dependent variables using the generalized estimating equation (GEE).

Dependent variable	Recurrent cough and wheezing	Recurrent cough without wheezing	Wheezing without recurrent cough
Predictor variables	OR (95% CI)	OR (95% CI)	OR (95% CI)
Rhinitis	2.47 (1.84, 3.30)	1.43 (1.03, 1.99)	1.30 (1.07, 1.58)
Sinusitis	1.54 (1.11, 2.14)	1.20 (0.80, 1.79)	1.41 (1.12, 1.77)
Sex (male = 1)	1.43 (1.06, 1.03)	0.87 (0.64, 1.20)	1.37 (1.10, 1.70)
Skin test positive (any)	1.90 (1.40, 2.60)	1.03 (0.74, 1.42)	1.50 (1.21, 1.86)
Asthma mother	2.22 (1.41, 3.49)	1.07 (0.60, 1.92)	1.67 (1.20, 2.34)
Asthma father	1.65 (1.10, 2.47)	1.75 (1.12, 2.73)	1.36 (0.97, 1.91)
Age	*	*	1.06 (1.04, 1.08)

Best fitting covariance pattern was selected using Quasi-likelihood Information Criterion (QIC). Study subjects were participants in the Children's Respiratory Study, Tucson Arizona.

*This variable was excluded from the model because it was not significant.

For example, a subject could report having active sinusitis during years 6 and 8 and then report not having it during years 11–18. The only restriction is that a subject must have the time-dependent covariate at each survey where they have the dependent variable.

The prevalence of recurrent cough with wheezing (Table 2) ranged from a high of 11.1% at the YR18 survey to a low of 7.9% at the YR13 survey, but remained approximately constant throughout the observational interval. In contrast, the proportions of subjects reporting recurrent cough with no wheezing were lower, with only 4.1% at YR13 and a maximum of 6.7% at YR16. A high proportion of subjects reported wheezing without recurrent cough, with values ranging from 27.2% at the YR18 survey to 12.5% at the YR8 survey. Rhinitis had the highest prevalence rates, ranging from 35.3% at the YR13 survey to a low of 20.2% at the YR18 survey.

Results obtained by fitting longitudinal models using GEE to the data on recurrent cough and/or wheezing are shown in Table 3. Both rhinitis and sinusitis were independent risk factors for recurrent cough and wheezing and for wheezing without recurrent cough. However, only rhinitis remained a significant (although just significant $P = 0.03$) risk factor for recurrent cough without wheezing in the final model. Male gender was a significant and independent risk factor for increased wheezing with and without recurrent cough, but was not significantly related to recurrent cough without wheezing. Both subjects who were classified as late skin test positive and those who were classified as persistent skin test positive were at increased risk of having recurrent cough and wheezing and of having wheezing without recurrent cough, with odds ratios that were very similar for both groups (results not shown). For this reason, both groups were combined and results for "any skin test positive" are shown in Table 3. Recurrent cough without wheezing was the only combination unrelated to skin test reactivity. The risk of wheezing without recurrent cough increased with age, as indicated by the significant age term.

Interactions between skin test reactivity and rhinitis and sinusitis were also tested. Since there is a very strong relationship between skin test reactivity and both rhinitis and sinusitis, these interactions were tested to estimate any synergistic effects. However, none were statistically significant suggesting that the contributions towards predicting recurrent cough and wheeze are indeed independent. Interactions between rhinitis and age were also included to test if the increased risk changed with time. However, these interactions were also not significant.

Risks associated with parental asthma were rather sporadic, with mother's asthma being a risk factor for wheezing with and without recurrent cough and father's asthma showing an increased risk of recurrent cough with and without wheezing. The inconsistency of the parental asthma as risk factors likely reflects complex interactions between genetic and environmental factors.

Discussion

There are three main findings of this study. First, rhinitis was significantly associated with recurrent

cough without wheezing. This effect was quite constant between the ages of 6 and 18; second, recurrent cough without wheezing was unrelated to allergic sensitization in our cohort; and third, wheezing with or without recurrent cough was significantly associated with rhinitis, and this effect was independent of allergic sensitization.

The results of our study suggest that rhinitis is an important determinant of recurrent cough during childhood. In children with no reported wheezing, the association appears to be unrelated to allergic sensitization and is thus most likely unrelated to a predisposition for asthma. In the case of children who do have reports of wheezing, on the contrary, the association between rhinitis and recurrent cough seems to be an expression of the well-established, strong link between rhinitis and asthma.

The factors that determine the association between recurrent cough and rhinitis in children who do not wheeze are not well understood. Several mechanisms have been suggested to explain how nasal dysfunction may affect the lower airway.[13,14] Post-nasal drip has been proposed as a major cause of recurrent cough.[5,15,16] Palombini and co-workers[17] identified a post-nasal drip syndrome in 45 of 78 adult patients suffering from chronic cough. Most of these patients met the criteria (including the presence of wheezing) to receive an asthma diagnosis, but in 17 subjects post-nasal drip was considered to cause chronic cough in the absence of asthma. Cough receptors have been found in the epithelium of the pharynx, larynx and trachea,[18,19] and it is plausible to surmise that these receptors may be hyper-responsive in individuals who present with rhinitis and concomitant recurrent cough. An indirect effect of nasal obstruction on the lower airways is also possible, as mouth breathing might reduce filtration, humidification and warming of the inhaled air, thus increasing the likelihood of recurrent cough. It is also possible that, together with the mechanical effects of post-nasal drip, passage of inflammatory cells and mediators from the nose into the lower airways may occur, and this may also be a source of chronic cough. Finally, the existence of a ''nasal-bronchial reflex'' has been postulated to explain the association between rhinitis and asthma,[13] but the role of such a reflex in determining cough has not been explored.

We found that children with recurrent cough but with no reports of wheeze were not more likely to be skin test positive than children without reports of wheeze or cough. These results confirm our previous findings from this same cohort based on surveys obtained between the ages of 2 and 6 years.[2] It thus appears that, even beyond the age of 6 years, the allergic mechanisms that are present in most children with asthma are not more likely to be present in children with recurrent cough and no wheeze. These data suggest that cough alone is not a frequent manifestation of asthma in this age group. This does not exclude the possibility, however, that cough may be the sole manifestation of asthma ''cough-variant asthma'' in a minority of children with recurrent cough, but this does not appear to be the main mechanism responsible for this form of recurrent cough in children.

A third finding of our study was, as stated earlier, that an association was found between rhinitis and wheezing with and without cough, and this association was independent of allergic sensitization. These findings are consistent with recent reports from our own group[8] and others[20,21] and suggest that, although the association between rhinitis and wheezing may be in part explained by IgE-mediated mechanisms, other processes seem to be at work that also have an influence on the development of wheezing in individuals with rhinitis. It is thus quite likely that some of the mechanisms discussed above that could explain the association between rhinitis and cough could also be involved in the association between rhinitis and wheezing. Specifically, nasal-bronchial reflexes, post-nasal drip of inflammatory cells and/or mediators, and absorption of inflammatory cells and/or mediators from the nose into the systemic circulation and ultimately the lung have been proposed to explain the association between rhinitis and asthma[13] and they could also explain the association between rhinitis and wheezing in this particular age group. Nevertheless, there is little doubt that IgE-mediated mechanisms play a crucial role in both rhinitis and wheezing in children, and the concomitant expression of such mechanisms in the nasal passages and in the central and lower airways may certainly explain, to a significant extent, the strong association we have found between these two clinical manifestations in childhood.

Even after adjusting for rhinitis, sinusitis was a significant risk factor for wheezing, both with and without recurrent cough. In contrast, sinusitis was not associated with recurrent cough in the absence of wheezing. Studies addressing the independent effect of sinusitis on asthma have shown contrasting results.[8,22–24] Differences between studies might be explained by the different way in which the presence of sinusitis was assessed, whether or not the effect of sinusitis was adjusted for rhinitis and whether the sample size was large enough to show an effect of sinusitis, independent of rhinitis. In our study, given the high prevalence rates of

rhinitis and its strong link with sinusitis, only a small proportion of sinusitis patients failed to report the presence of rhinitis, leading to some concern about our statistical power in the small group of children with recurrent cough alone. Alternatively, it is possible that specific mechanisms, such as the existence of a pharyngobronchial reflex[25] or a reduction in nitric oxide in the upper airways,[26] may be involved in the relation of sinusitis to wheezing but not to recurrent cough. Whether the impact of sinusitis on asthma is independent of rhinitis or related to it, there is little doubt that asthma symptoms may improve after sinusitis treatment, as shown in several clinical trials.[27,28]

In this framework, our findings may have important clinical implications in the prevention and clinical management of asthma and recurrent cough. There is solid evidence that treatment of rhinitis is beneficial to co-existing asthma symptoms. In a study by Watson and colleagues,[29] patients with perennial allergic rhinitis and asthma had a significant reduction of their bronchial hyperresponsiveness and evening asthma symptom scores when treated with intranasal steroid therapy. Similar beneficial effects of intranasal steroid solutions on asthma symptoms and bronchial hyper-responsiveness have been shown in several other clinical studies.[30–32] A direct deposition of the steroid solution in the lung is an unlikely explanation for these findings, since some of these studies[29,30] have shown experimentally that only about 2% of the drug particles were in the easily respirable range and deposited in the chest area. Based on the existing evidence, an integrated treatment strategy targeting both upper and lower airways has been advocated for[33] and should be considered for all patients with co-existing rhinitis and asthma.

Similarly, our findings suggest that an upper airway evaluation should be an essential part of the clinical management of patients with chronic cough. Recurrent cough is frequently a troublesome symptom during the growing years, and in the case of cough alone, the factors that determine it are difficult to identify, making the treatment of this condition particularly challenging. Faniran et al.[34] found that, even if they did not appear to be affected by ''cough-variant asthma'', many children with persistent cough were treated with anti-asthma medications, which are often not beneficial in the presence of cough alone without other evidence of airway obstruction. In support of this assumption, Chang et al.[35] reported the results of a randomized, double blind, placebo-controlled clinical trial among 43 children with recurrent cough. These authors reported no effect of either albuterol or beclomethasone on cough frequency or cough scores in these children. It is likely that a proportion of these cases might benefit from a thorough clinical assessment of co-existing rhinitis/sinusitis. However, in what proportion of children with cough alone and to what extent the treatment of rhinitis/sinusitis symptoms may be beneficial remains to be determined.

It also remains to be determined whether an early treatment of upper airway diseases may reduce significantly the risk of developing ''new'' asthma and/or recurrent cough. From a public health standpoint, this is an issue of primary importance. Our study did not address the temporal relationship between rhinitis and lower airway symptoms, but previous epidemiological evidence supports the hypothesis that rhinitis frequently precedes the onset of asthma[8,36,37] and/or recurrent cough.[38] These findings argue for an early treatment of upper airway symptoms in children with rhinitis/sinusitis and for monitoring these patients, particularly if allergic, over time for onset of respiratory symptoms and bronchial hyper-responsiveness.

One of the limitations of the current study is related to missing observations. Longitudinal models like the GEE assume that any missing observations are missing completely at random. Clearly in a large epidemiological study like the CRS that spans an 18 year period this is not the case. Most missing observations are related to the natural attrition of subjects moving away or later refusing to participate. It is also been demonstrated that subjects with respiratory diseases or symptoms will be less likely to drop out of a study. This suggests that the estimated prevalence rates and potential risk factors of recurrent cough and wheeze may in fact overestimate the true population values. Another potential limitation could be that we did not include recurrent cough from the earlier surveys. However, we elected to not include recurrent cough or wheeze for years 2 and 3 since it was felt that these symptoms in early life represent a different phenotype. To insure that there was no confounding, binary variables representing early wheeze and early recurrent cough were added to the final models and the results were not substantially altered (results not shown).

In conclusion, we found that recurrent cough without wheeze was significantly associated with the presence of rhinitis during childhood, as was also wheezing with or without cough. As compared with wheezing with or without cough, cough alone showed different patterns of association with different risk factors, suggesting that this

symptom, when present independent of wheezing, may be a specific phenotype. Our data also suggest that evaluation of upper airways should be considered in any child with recurrent cough.

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